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<p>97-554679/51 B05 SAGA 96.04.02 SAGAMI CHEM RES CENTRE *JP 09268153-A 96.04.02 96JP-079970 (97.10.14) C07C 49/227, A61K 31/23 Trifluoromethyl ketone deriv. and phospholipase A2 inhibitor - useful in treatment of inflammatory diseases e.g. as antiinflammatory or antiallergic drug. C97-177310</p>	<p>B(10-F2, 14-C3, 14-D7A, 14-G2A) .4 B0290</p>
<p>Trifluoromethyl ketone deriv. of formula RCOCF_3, where RCO is acyl residue of n-3 series highly unsatd. fatty acid is new.</p> <p>Also claimed is the drug and/or cytoplasmic phospholipase A₂ (cPLA₂) inhibitor contg. trifluoromethyl ketone deriv. of formula RCOCF_3.</p> <p><u>USE</u> The trifluoromethyl ketone deriv. is new, has phospholipase A2 inhibitory activity, and is useful as drug.</p> <p><u>ADVANTAGE</u> The trifluoromethyl ketone deriv. has excellent cPLA₂ inhibitory activity, and is useful in treatment of inflammatory diseases e.g. as antiinflammatory or antiallergic drug.</p>	<p><u>PREPARATION</u> The trifluoromethyl ketone deriv. of formula RCOCF_3 can be prepd. e.g. by treatment of n-3 series highly unsatd. fatty acid with halogenating agent (e.g. oxalyl chloride) to give corresponding acid halide, followed by reaction with trifluoroacetic acid anhydride in the presence of base (e.g. pyridine) in a conventional manner (e.g. Tetrahedron Letters, 33, 1285 [1992]).</p> <p><u>EXAMPLE</u> Docosahexaenic acid (164 mg) in 2 ml THF contg. half drop of DMF was reacted with 0.44 ml oxalyl chloride at room temp. for 2 hr., and the resultant acid chloride in 5 ml dichloromethane was reacted with 0.42 ml trifluoroacetic anhydride in the presence of 0.32 ml pyridine at 0°C for 1 hr. and conventionally worked up followed by chromatography over silica gel to give 56 mg (32 % yield) of docosahexaenoyltrifluoromethane (DHA-CF₃).</p> <p>DHA-CF₃ and eicosapentaenoyltrifluoromethane (EPA-CF₃) were tested on cPLA₂ inhibitory activity by cell-free reaction with cPLA₂ in a mixt. of 1M-tris-HCl (pH 9.0), 2 % FBS-added albumin (25:12.5 JP 09268153-A+</p>

μL) and 50 mM calcium chloride soln. (20 μL) at 37°C for 20 min.
followed by reaction with 0.5 nmol 1-palmitoyl-2-[14C]-arachidonoyl-
glycerophosphoethanolamine at 37°C for 20 min. and determination
of radioactivity of free fatty acid fraction; or by cellular reaction with
neutrophile (prepd. by differentiation from human myelocytic
leukemia HL60 followed by cultivation in the presence of 1-[14C]-
arachidonic acid) at 37°C for 5 min. in the presence of A23187
followed by determination of radioactivity of free fatty acid fraction,
in comparison with arachidonoyltrifluoromethane (AA-CF₃) and
palmitoyltrifluoromethane (PA-CF₃), to give following results (Cpd.,
concn. (μM)/[14C]-arachidonic acid relative production (%) in: cell-
free/cellular system):
None, -/100.00/100.00; DHA-CF₃, 1/35.2, 30/33.81; EPA-CF₃,
1/28.56, 30/14.16; AA-CF₃, 1/20.83, 30/21.24; and PA-CF₃,
30/101.16.(PHP).
(5pp038DwgNo.0/0)

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